EXECUTIVE SUMMARY

2-Ethylhexanol – Oral Risk Assessment CAS # 104-76-7			
PARAMETER	**LEVEL**	**UNITS**	**DERIVED**
NOAEL (no-observed-adverse-effect level)	36	mg/kg-day	From a 104-week gavage study in F344 rats
Oral RfD (oral reference dose)	0.1	mg/kg-day	From a 104-week gavage study in F344 rats with a 300x total uncertainty factor
TAC (total allowable concentration)	0.8	mg/L	For a 70 kg adult drinking 2 L/day using a 20% relative source contribution for drinking water
SPAC (single product allowable concentration)	0.08	mg/L	From the TAC, using the default 10 sources of 2-ethylhexanol in drinking water
STEL (short term exposure level)	3	mg/L	From a 13-week gavage study, for a 10 kg child drinking 1 L/day

KEY STUDY	Astill, B. D., Gingell, R., Guest, D., Hellwig, J., Hodgson, J.R., Kuettler, K., Mellert, W., Murphy, S.R., Sielken, R.L., and Tyler, T.R. (1996b). Oncogenicity testing of 2-ethylhexanol in Fischer 344 rats and B6C3F1 mice. Fundam Appl Toxicol 31(1): 29-41
CRITICAL EFFECT	Repeated gavage exposure to 2-ethylhexanol in rats and mice was associated with a reduction in mean body weight of 10% or greater, and altered organ weights compared to controls.
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD include: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 1x for subchronic to chronic extrapolation • 1x for LOAEL to NOAEL • 3x for database deficiencies The total uncertainty factor is therefore 300x.
TOXICITY SUMMARY	Repeated gavage exposure with 2-ethylhexanol was associated with reductions in body weight and altered organ weights in rats and mice in the absence of specific organ toxicity. Rats were more sensitive than mice, since the body weight reduction occurred at lower dose levels in rats. Developmental toxicity after 2-ethylhexanol included skeletal malformation and retardation, with reduced fetal body weight accompanied by signs of toxicity in dams. The weight of genotoxic evidence suggests that 2-ethylhexanol is not mutagenic or clastogenic. Lifetime exposure of female mice to 2-ethylhexanol by gavage caused increased hepatocellular carcinomas that exceeded the concurrent control, but was within the historical control range for gavage studies reported by the NTP. There was no significant difference in hepatocellular adenomas or carcinomas in treated male mice or male or female F344 rats. 2-Ethylhexanol is a peroxisome proliferator, and this mode of action may be related to or influence the development of hepatocellular carcinomas. While some rodents are highly susceptible to peroxisome proliferation, humans and other primates are resistant. It was concluded that the *data are inadequate for an assessment of human carcinogenic potential* under U.S. EPA (2005) guidelines.
CONCLUSIONS	2-Ethylhexanol exposure was associated with a dose-dependent reduction in mean terminal body weight in repeat dose studies in animals. Signs of developmental toxicity after oral and dermal exposure to 2-ethylhexanol were seen at doses that elicited maternal toxicity. Reduced mean terminal body weight in the chronic gavage study in rats was determined to be the critical effect. Based on the selection of the most sensitive endpoint as the critical effect, in the most sensitive species and sex, the drinking water TAC, SPAC, and STEL levels herein are protective of public health.